UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,191	06/24/2005	Jeffrey P. Erickson	AIB-09206	5158

7590 08/02/2006

Peter G Carroll
Medlen & Carroll
101 Howard Street
Suite 350
San Francisco, CA 94105

EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/505,191	ERICKSON, JEFFREY P.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-29,32-35 and 41-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 15-29, 32-35, 41-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13, 15-29, 32-35, 41-50 are pending and under consideration. Claims 14, 30-31, 36-40, are canceled.

Withdrawn Rejections

Applicant's arguments, see page 16-17, filed 05/11/06, with respect to the rejection of claims 2-4, 14-15, 23, 25-26, and 29, 32-35 under 35 U.S.C. 2nd paragraph have been fully considered and are persuasive. The rejection of claims 2-4, 14-15, 23, 25-26, and 29, 32-35 has been withdrawn.

Applicant's arguments, see page 17, filed 05/11/06, with respect to the priority designation of the application have been fully considered and are persuasive. The request for a priority statement for insertion as the first paragraph of the Applicant's specification has been withdrawn.

Applicant's arguments, see page 11, filed 05/11/06, with respect to the rejection of claims 29-30 under 35 U.S.C. 112 & 1st paragraph as failing to comply with written description requirement been fully considered and are persuasive. The rejection of claims 29-30 has been withdrawn.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15-29, 32-35, 41-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an exogenous nucleic cid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting transcription control region, does not reasonably provide enablement for a transgenic non-human mammal by way of the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic non-human mammal expressing a polypeptide in saliva at a level of at least 0.5 mg/ml, a method of collecting saliva from the same transgenic non-human mammal, and a method of producing the same transgenic non-human mammal.

The specification has asserted that the invention features transgenic non-human mammals that express transgenic polypeptides in their saliva. The specification discusses that salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest. See pages 26-28 of the specification. However, the guidance provided by the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals embraced by the claims. Moreover, the guidance provided by the specification is general as it does not even disclose which saliva regulatory elements could be used to create any of the transgenic non-human mammals embraced by the claims. Finally, the working examples provided by the specification (see pages 81-101) while exemplifying creation of different transgenic cows that express prothrombin and fibrinogen in their saliva respectively, did not disclose which saliva regulatory elements were used to create the transgenic cows and therefore failed to provide the skilled artisan with adequate guidance to make any of the transgenic non-human mammals embraced by the claims. Given the lack of guidance provided by the specification it would have required

undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a first issue, the claims embrace transgenic non-human mammals that express and produce a transgenic polypeptide in saliva. The specification has discussed that saliva specific regulatory elements are necessary to achieve expression of a polypeptide of interest in saliva of a transgenic non-human mammal. See pages 26-29 of the specification. However, the guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (from PSP and B1-Ips genes) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson. Finally, in an attempt to provide guidance as to which saliva regulatory sequence may be used within the scope of the claimed invention, the specification has relied on improper incorporation by reference of subject matter that appears to be essential. See the references to Mikkelsen, Larson and Mirels at pages 27-28 of the specification. Applicant is reminded that subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. See 37 C.F.R. 1.57(c) and MPEP 608.01(p). Accordingly, given the lack of guidance provided by the specification, the skilled artisan would not know which regulatory sequence to use to achieve

saliva specific expression of a polypeptide in a transgenic non-human mammal. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use any of the transgenic non-human mammals embraced by the claims without a reasonable expectation of success.

As a second issue, while the claims embrace transgenic non-human mammals expressing a transgenic polypeptide in saliva, the working examples provided by specification did not provide adequate guidance that would enable one of skill in the art to create any of the transgenic non-human mammals embraced by the claims. The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva. However, the working examples failed to disclose which saliva regulatory elements were used in the creation the transgenic cows. As previously stated the specification as a whole has not even identified or provided the regulatory elements necessary to practice the claimed invention. A mere statement that saliva regulatory elements existed and could be used is not sufficient to enable the breadth of the claims as directed to transgenic non-human mammals expressing transgenic polypeptides in saliva. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. In this case the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims.

As a final issue, the claims embrace transgenic non-human mammals that produce transgenic polypeptides in saliva. As written the claims did not convey germline transmission of the transgene and can be broadly interpreted to read on a transgenic non-human mammal

having a single cell expressing a transgene in saliva. It would be unpredictable if expression of a transgene in a single cell of a transgenic non-human mammal correlated to expression and collection of a transgenic polypeptide in saliva, particularly since expression of a transgenic polypeptide in a single cell would not result in a collectable amount of the polypeptide. Moreover it is unpredictable if a transgenic non-human mammal that expressed a transgene in a single cell could be used in the claimed methods because it would appear that the claimed methods would require the transgene to be expressed in every cell of the salivary gland, in particular because it would be unpredictable if a single cell, which expresses the transgene could produce sufficient levels of a transgenic polypeptide for practicing the invention as claimed, and more particularly because the claims require the transgenic polypeptide to produced at a level of 0.5mg/ml.

Alternatively, the claims may be interpreted to read somatic cell gene transfer, wherein the cells of the salivary glands of non-human mammals have been administered vectors comprising nucleic acid molecules encoding a polypeptide of interest. Such an interpretation of the claims would result in both salivary specific and/or systemic polypeptide expression depending on which promoter is used. The prior art in fact teaches that salivary glands may be used as an entry point for introduction of gene therapy type expression vectors into a subject to obtain systemic expression of therapeutic polypeptides. See Baum et al (Trends in Molecular Medicine, 2004, 10(12): 585-590), for examples on pages 587-588. If for example, the polypeptide of interest is thrombin then systemic expression would probably kill the transgenic non-human mammal as a result of massive blood clotting throughout the non-human mammal. Therefore it would be unpredictable if transgenic non-human mammals created by somatic cell gene transfer to the salivary gland could be created and used in accordance with the invention as claimed.

Given, the lack of guidance and absence of working examples provided by the specification correlating to creation of transgenic non-human mammals, the lack of guidance provided by the specification with respect to use of saliva regulatory elements, the unpredictability of saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Response to Arguments

Applicant's arguments filed 05/11/06 have been fully considered but they are not persuasive. Applicants disagree to Examiner's statement that the guidance provided by the specification does not correlate to use of any particular saliva regulatory element for the creation of transgenic non-human animals (Remarks p 8). Applicants point out that several salivary promoters are discussed and exemplified and Applicants direct the attention to various recitations in the specification as for example "among particular preferred control regions in this regards are those of genes of the multigene family of proline-rich proteins (PRP), in particular the promoters of PRP genes (Remarks p 8). Applicants further point to the specification wherein it is recited for example "The mouse PSP gene has been cloned and characterized by Shaw and Schibler and for example genes for rat salivary-gland B1-immunoreactive proteins of adult (and neonatal) rat sublingual and parotid glands ..... the transcriptional control elements of these genes, and their homologs and paralogs are suitable to engineer salivary gland... expression of genes". Applicants argue that the Examiner has been distracted by the "incorporation by reference" for some non-patent publications mentioned in the Applicant's specification (Remarks, p 9-10).

In response this is not found persuasive because in determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make

and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise. These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled. Applicants have not provided guidance to overcome the unpredictability of saliva regulatory elements, and it would have required undue experimentation for the skilled artisan to practice the claimed invention. As Samuelson notes a number of number of genes that code for abundant salivary proteins have been cloned, including genes that are predominantly expressed in a single salivary gland, such as Psp, the exact positions and nature of the salivary-specific regulatory sequences have not been fully characterized (Samuelson (Annu Rev Phys, 1996, 58: 209-229) (p 214, last paragraph). Samuelson also notes that transgenic expression studies are needed to describe the sequences, as well as to define easily manipulated promoter/enhancer fragments for transgenic experiments designed to alter the physiology of the salivary glands through the

expression of specific transgenes (p 214 last paragraph, p215, 1st paragraph). Samuelson further notes that although PSP is the most abundant protein secreted from the mouse parotid gland, its function in the oral cavity remains obscure (p 217, 1st paragraph). Samuelson while reviewing the status of the inducible expression of a proline-rich protein promoter notes that transgene expression would be silent until the animals were fed tannins or treated with b1-adrenergic stimulants, which would allow for the analysis of transgenes that are toxic to the mice or for the evaluation of the acute affects of the expression of a particular protein in the salivary gland (p 218, 1st paragraph). Applicants have not provided guidance to override the unpredictability of creating said transgenic

Applicants argue that the Applicant has enabling support for the production of a transgenic mammal in view of Doeber et al, and Krimpenfort et al, references by incorporation (Remarks p 10-11). Applicants point to the disclosure of prothrombin nucleic acid sequence Accession No. J00307, in the Applicant's specification wherein this sequence combined with Holy et al, "Methods for producing thrombin" provide enablement for the Applicant's claimed embodiments (Remarks, p 9-11).

In response this is not found persuasive because the breadth of the claims is directed to a transgenic non-human mammal whose genome comprises an exogenous nucleic acid encoding at least one transgenic polypeptide, herein the nucleic acid is operably linked to a salivary gland-specific cis-acting transcription control region, wherein the polypeptide is produced at a level at least 0.5 mg/ml. Samuelson notes that the methods for transforming the germilne of other mammals are not widely and ES cell transgenic technology is available only in the mouse (p 212, 2nd paragraph).

As such the rejections of claims 1-13, 15-29, 32-35, 41-50 are maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-8, 10-13, 15-19 rejected under 35 U.S.C. 102(b) as anticipated by **Mikkelsen et al,** (Nucleic Acid Research, 20(9): 2249-2255, 1992).

Mikkelsen teaches transgenic mouse whose genome comprises an exogenous nucleic acid encoding the human blood coagulation factor VIII-C terminal peptide, wherein said nucleic acid operably linked to salivary gland specific transcription control region (p 2250, 2nd column, figure 2 and p 2253, figure 6). Mikkelsen teaches the polypeptide is expressed in the parotid and salivary glands of the transgenic mouse and the polypeptide is secreted in samples of collective saliva wherein said transgenic polypeptide is human and comprises the active and proactive form and wherein the transgenic polypeptide comprises activity relative to that of naturally occurring polypeptide (p 2253, figure3 panel B). Mikkelsen also teaches that a considerable amount of FVII polypeptide was found in the saliva from the transgenic lines transcribing the construct (p 2254, 4th paragraph). The expressing lines secrete an amount of FVIII light chain per salivation (about 0.05 ml of saliva) of about 10 units, which corresponds to the amount of FVIII in 10 ml of normal human plasma (p 2254, 4th paragraph). Mikkelsen teaches a salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of the transgenic mouse and the transgene is a blood protein (p 2254, 1st column and p 2251, figure 3 and p 2252, figure 4).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-5, 29, and 32-35** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lubon et al,** (US. 5,880,327) in view of **Mikkelsen et al,** (Nucleic Acid Research, 20(9): 2249-2255, 1992).

Lubon teaches the production of transgenic mammals, including, cows, goats, sheep, and pigs expressing human blood coagulation **Factor VIII** (FVIII) in milk. Since the mouse of Mikkelsen contains a construct indistinguishable from the claimed cows, goats, sheep, and pigs or horses of claims 2-5, the mammals of claims 2- would reasonably be expected to produce FVIII at the same levels as Mikkelsen's mice. A product and its properties cannot be separated. Lubon offers motivation for using mammals producing large volumes of body fluids in stating an important need remains for an efficient and relatively inexpensive means of producing large quantities of infectious-free, human F8 protein suitable for clinical use (column 2, lines 35-37). Lubon offers motivation since the transgenic animal system they described produces human F8 recombinantly satisfies this need (column 2, lines 39-40).

Mikkelsen teaches transgenic mouse expressing human F8 under the control of PSP promoter, where the mouse produces detectable quantities of F8 in its saliva.

Thus, at the time of the claimed invention it would have been obvious to the skilled artisan to make a cow, sheep, goat, pig or horses expressing F8 in its salivary gland each of which produces large volumes of saliva than mice given the teachings of Lubon in view of Mikkelsen teaching the production of mice expressing F8 in its saliva.

Claims **1, 16-18, 20-28** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lubon et al,** (US. 5,880,327) in view of **Mikkelsen et al,** (Nucleic Acid Research, 20(9): 2249-2255, 1992); **Coppes et al,** (Radiation Research, 153: 339-346, 2000).

Lubon teaches the production of transgenic mammals, including, cows, goats, sheep, and pigs expressing human blood coagulation **Factor VIII** (FVIII) in milk. Since the mouse of Mikkelsen contains a construct indistinguishable from the claimed cows, goats, sheep, and pigs or horses of claims 2-5, the mammals of claims 2- would reasonably be expected to produce FVIII at the same levels as Mikkelsen's mice. A product and its properties cannot be separated. Lubon offers motivation for using mammals producing large volumes of body fluids in stating an important need remains for an efficient and relatively inexpensive means of producing large quantities of infectious-free, human F8 protein suitable for clinical use (column 2, lines 35-37). Lubon offers motivation since the transgenic animal system they described produces human F8 recombinantly satisfies this need (column 2, lines 39-40).

Mikkelsen teaches transgenic mouse whose genome comprises an exogenous nucleic acid encoding the human blood coagulation factor VIII-C terminal peptide, wherein said nucleic acid operably linked to salivary gland specific transcription control region (p 2250, 2nd column, figure 2 and p 2253, figure 6). Mikkelsen teaches the polypeptide is secreted in the saliva wherein said transgenic polypeptide is human and comprises the active and proactive form and wherein the transgenic polypeptide comprises activity relative to that of naturally occurring polypeptide (p 2253, figure 3, panel B). Mikkelsen also teaches that a considerable amount of FVII polypeptide was found in the saliva from the transgenic lines transcribing the construct (p 2254, 4th paragraph). The expressing lines secrete an amount of FVIII light chain per salivation (about 0.05 ml of saliva) of about 10 units, which corresponds to the amount of FVIII in 10 ml of

normal human plasma (p 2254, 4th paragraph). Mikkelsen teaches a salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of the transgenic mouse and the transgene is a blood protein (p 2254, 1st column and p 2251, figure 3 and p 2252, figure 4).

Coppes teaches the insertion of a duct cannula made from Medical Grade Silicone Tubing inserted into the parotid glands of rats after a small incision (p 340).

Thus, at the time of the claimed invention it would have been obvious to the skilled artisan to make a cow, expressing prothrombin in its salivary gland using the tubing technology of Coppes each of which produces large volumes of saliva than mice given the teachings of Lubon in view of Mikkelsen teaching the production of mice expressing F8 in its saliva.

Claims **29, 32-35** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mikkelsen et al,** (Nucleic Acid Research, 20(9): 2249-2255, 1992) in view of **Lubon et al,** (US. 5,880,327).

Mikkelsen teaches transgenic mouse whose genome comprises an exogenous nucleic acid encoding the human blood coagulation factor VIII-C terminal peptide, wherein said nucleic acid operably linked to salivary gland specific transcription control region (p 2250, 2nd column, figure 2 and p 2253, figure 6). Mikkelsen teaches the polypeptide is secreted in the saliva wherein said transgenic polypeptide is human and comprises the active and proactive form and wherein the transgenic polypeptide comprises activity relative to that of naturally occurring polypeptide (p 2253, figure 3, panel B). Mikkelsen also teaches that a considerable amount of FVII polypeptide was found in the saliva from the transgenic lines transcribing the construct (p 2254, 4th paragraph). The expressing lines secrete an amount of FVIII light chain per salivation (about 0.05 ml of saliva) of about 10 units, which corresponds to the amount of FVIII in 10 ml of

normal human plasma (p 2254, 4th paragraph). Mikkelsen teaches a salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of the transgenic mouse and the transgene is a blood protein (p 2254, 1st column and p 2251, figure 3 and p 2252, figure 4). Mikkelsen differs from the claimed invention by not teaching salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of a transgenic cow.

Lubon teaches the production of transgenic mammals, including, cows, goats, sheep, and pigs expressing human blood coagulation Factor VIII (FVIII) in milk. Since the mouse of Mikkelsen contains a construct indistinguishable from the claimed cows, the mammals of claims 32-35 would reasonably be expected to produce FVIII at the same levels as Mikkelsen's mice. A product and its properties cannot be separated. Lubon offers motivation for using mammals producing large volumes of body fluids in stating an important need remains for an efficient and relatively inexpensive means of producing large quantities of infectious-free, human F8 protein suitable for clinical use (column 2, lines 35-37). Lubon offers motivation since the transgenic animal system they described produces human F8 recombinantly satisfies this need (column 2, lines 39-40).

Claims **41-47** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mikkelsen et al,** (Nucleic Acid Research, 20(9): 2249-2255, 1992) in view of **Lubon et al,** (US 5,965,789).

Mikkelsen teaches transgenic mouse whose genome comprises an exogenous nucleic acid encoding the human blood coagulation factor VIII-C terminal peptide, wherein said nucleic acid operably linked to salivary gland specific transcription control region (p 2250, 2nd column, figure 2 and p 2253, figure 6). Mikkelsen teaches the polypeptide is secreted in the saliva

wherein said transgenic polypeptide is human and comprises the active and proactive form and wherein the transgenic polypeptide comprises activity relative to that of naturally occurring polypeptide (p 2253, figure 3, panel B). Mikkelsen also teaches that a considerable amount of FVII polypeptide was found in the saliva from the transgenic lines transcribing the construct (p 2254, 4th paragraph). The expressing lines secrete an amount of FVIII light chain per salivation (about 0.05 ml of saliva) of about 10 units, which corresponds to the amount of FVIII in 10 ml of normal human plasma (p 2254, 4th paragraph). Mikkelsen teaches a salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of the transgenic mouse and the transgene is a blood protein (p 2254, 1st column and p 2251, figure 3 and p 2252, figure 4). Mikkelsen differs from the claimed invention by not teaching salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of a transgenic cow.

Lubon teaches a mouse expressing human **prothrombin** and F8 under the control of the WAP promoter, where the mouse produces detectable quantities prothrrombin in its saliva (column 5, lines 13-18).

Thus, at the time of the claimed invention it would have been obvious to the skilled artisan to make a cow, expressing prothrombin in its salivary gland each of which produces large volumes of saliva than mice given the teachings of Lubon in view of Mikkelsen teaching the production of mice expressing F8 in its saliva.

Claims **48-50** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mikkelsen et al,** (Nucleic Acid Research, 20(9): 2249-2255, 1992) in view of **Lubon et al,** (US 5,965,789); **Coppes et al,** (Radiation Research, 153: 339-346, 2000).

Mikkelsen teaches transgenic mouse whose genome comprises an exogenous nucleic acid encoding the human blood coagulation factor VIII-C terminal peptide, wherein said nucleic acid operably linked to salivary gland specific transcription control region (p 2250, 2nd column, figure 2 and p 2253, figure 6). Mikkelsen teaches the polypeptide is secreted in the saliva wherein said transgenic polypeptide is human and comprises the active and proactive form and wherein the transgenic polypeptide comprises activity relative to that of naturally occurring polypeptide (p 2253, figure 3, panel B). Mikkelsen also teaches that a considerable amount of FVII polypeptide was found in the saliva from the transgenic lines transcribing the construct (p 2254, 4th paragraph). The expressing lines secrete an amount of FVIII light chain per salivation (about 0.05 ml of saliva) of about 10 units, which corresponds to the amount of FVIII in 10 ml of normal human plasma (p 2254, 4th paragraph). Mikkelsen teaches a salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of the transgenic mouse and the transgene is a blood protein (p 2254, 1st column and p 2251, figure 3 and p 2252, figure 4). Mikkelsen differs from the claimed invention by not teaching salivary gland-specific expression construct wherein the transgene is expressed in the parotid and salivary glands of a transgenic cow.

Lubon teaches a mouse expressing human **prothrombin** and F8 under the control of the WAP promoter, where the mouse produces detectable quantities prothrrombin in its saliva (column 5, lines 13-18).

Coppes teaches the insertion of a duct cannula made from Medical Grade Silicone Tubing inserted into the parotid glands of rats after a small incision (p 340).

Thus, at the time of the claimed invention it would have been obvious to the skilled artisan to make a cow, expressing prothrombin in its salivary gland each of which produces large volumes of saliva than mice given the teachings of Lubon in view of Mikkelsen teaching

the production of mice expressing F8 in its saliva and in view of Coppes teaching the insertion of a flexible tubing into the parotid gland of mice for collecting the transgenic saliva.

Conclusion

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Stagias, Ph.D.
Art Unit 1632

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630